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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte MARY R. FLACK, RICHARD KNAZEK,
and MARCUS REIDENBERG

Appeal 2009-1290
Application 10/806,088
Technology Center 1600

Decided:[1] February 20, 2009

Before ERIC GRIMES, RICHARD M. LEBOVITZ, and
FRANCISCO C. PRATS, *Administrative Patent Judges*.

GRIMES, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a method of treating cancer with gossypol. The Examiner has rejected the claims

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[1] The two-month time period for filing an appeal or commencing a civil action, as recited in 37 C.F.R. § 1.304, begins to run from the decided date shown on this page of the decision. The time period does not run from the Mail Date (paper delivery) or Notification Date (electronic delivery).

as obvious over the prior art. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

STATEMENT OF THE CASE

This appeal arises out of an application for reissue of U.S. Patent 6,114,397, originally issued Sept. 5, 2000. The '397 patent discloses that "[g]ossypol is a double biphenolic compound derived from crude cottonseed oil . . . which has been used extensively as a male contraceptive in China" ('397 patent, col. 1, ll. 18-21). The '397 patent describes administration of gossypol to human patients for treatment of cancer (*id.* at col. 6, l. 17 to col. 7, l. 21).

Claims 8-14, 16, and 38-43 are pending and on appeal. The claims subject to each rejection have not been argued separately and therefore stand or fall together. 37 C.F.R. § 41.37(c)(1)(vii). Claims 8 and 13 are representative and read as follows (additions and deletions to original claim 8 indicated by underlining and brackets, respectively):

8. A method for treating a cancer in a human, wherein the cancer is susceptible to treatment with gossypol, a [pharmaceutically] physiologically acceptable salt of gossypol, or a combination thereof, which method comprises:

administering to said human a composition comprising an anti-cancer effective amount of at least one compound selected from the group consisting of gossypol and a physiologically acceptable salt thereof, [and] wherein the at least one compound is administered with a pharmaceutically acceptable carrier, and wherein the at least one compound exhibits an overall effect of rotating the plane of polarized light in the (-) direction.

13. The method of claim 8, wherein said compound is administered orally at a dose of 20-100 mg/d.

The Examiner relies on the following evidence:

Zhang et al. (Zhang), "Comparison of the Killing Effect of Levorotatory, Dextrorotatory and Racemic Gossypol on HeLa Cells," 7 Acta Academiae Medicinae Sinicae 384-387 (1985).

Band et al. (Band '86), "Cytocidal Effects of Gossypol and its Optical Isomers on Reproductive Cancer Cell Lines," 23 Gynecologic Oncology 261 (1986).

Wu et al. (Wu '86), "Pharmacokinetics of (±)-, (+)-, and (–)-gossypol in humans and dogs," 39 Clin. Pharmacol. Ther. 613-618 (1986).

Wu et al. (Wu '89), "An *in Vitro* and *in Vivo* Study of Antitumor Effects of Gossypol on Human SW-13 Adrenocortical Carcinoma," 49 Cancer Research 3754-3758 (1989).

Appellants rely on the following evidence:

Band et al. (Band '89), "Antiproliferative Effect of Gossypol and Its Optical Isomers on Human Reproductive Cancer Cell Lines," 32 Gynecologic Oncology 273-277 (1989).

Declaration under 37 C.F.R. § 1.132 of Marcus Reidenberg, filed May 12, 2005.

Declaration under 37 C.F.R. § 1.132 of Jon Theodore Holmlund, filed Oct. 20, 2006.

The claims stand rejected under 35 U.S.C. § 103(a) as follows:

- Claims 8-10, 16, and 38-43 based on Wu '89, Band '86, and Zhang; and
- Claims 11-14 based on Wu '89, Band '86, Zhang, and Wu '86.

OBVIOUSNESS

The Issue

The Examiner has rejected claims 8-10, 16, and 38-43 as obvious in view of Wu '89, Band '86, and Zhang. The Examiner's position is that the

prior art would have suggested administering (–)-gossypol to human patients to treat cancer, and would have provided those skilled in the art with a reasonable expectation that the treatment would be successful.

Appellants contend that those of ordinary skill in the art would not have had a reasonable expectation that gossypol could be used successfully to treat cancer in human patients.

The issue is: Did the Examiner err in concluding that the prior art would have provided a reasonable expectation of success in administering (–)-gossypol to treat cancer in human patients?

Findings of Fact

1. Claim 8 is directed to a method of treating cancer in humans by administering gossypol (or a physiologically acceptable salt of it) that "exhibits an overall effect of rotating the plane of polarized light in the (–) direction" (claim 8).

2. The gossypol enantiomer recited in claim 8 is also known in the art as (–)-gossypol and levorotatory gossypol (see Zhang 384).

3. The complementary gossypol enantiomer is known in the art as (+)-gossypol or dextrorotatory gossypol (see *id.*).

4. A mixture of (–)-gossypol and (+)-gossypol is known in the art as (±)-gossypol or racemic gossypol (see *id.*).

5. Wu '89 discloses injection of nude mice with SW-13 cells (Wu '89 3755, left-hand col.).

6. SW-13 cells are human adrenocortical carcinoma cells (*id.* at 3754, right-hand col.).

7. Wu '89 discloses that the mice injected with SW-13 cells were treated with gossypol (*id.* at 3755, left-hand col.).

8. Wu '89 discloses that "[g]ossypol was shown to suppress the proliferation of SW-13 human adrenocortical carcinoma cells" and that "[e]stablished tumors were also shown to respond to gossypol treatment" (*id.* at 3757, right-hand col.).

9. Wu '89 concludes that "gossypol appeared to be safe and effective in delaying growth of SW-13 cells in nude mice" (*id.*).

10. Wu '89 states that "[t]hese data suggest that gossypol may provide a beneficial effect in patients with adrenocortical carcinoma by decreasing the overall tumor burden and prolonging their duration of survival" (*id.* at 3758, left-hand col.).

11. Wu '89 does not state that the gossypol used had been resolved into (+)- and (–)-enantiomers.

12. Band '86 discloses that "gossypol at micromolar concentrations . . . inhibits the growth and has cytocidal effects on a variety of reproductive cancer cell lines of male and female origin" (Band '86 261).

13. Band '86 discloses that seven cancer cell lines "were significantly . . . more sensitive to gossypol (0.90-1.78 μg/ml) than normal human cells of high mitotic activity . . . and low mitotic activity" (*id.*).

14. Band '86 discloses that the "tumor growth inhibitory activity of gossypol, which is a racemic mixture of its optical isomers[,] is primarily attributable to the (–)-isomer which is 3.6–9.3 times more potent than the (+)-isomer" (*id.*).

15. Band '86 concludes that, "[c]onsidering the established absence of side effect in the administration of low doses of gossypol to humans, these data suggest that (–)-gossypol, alone or in combination with other drugs, may be useful clinically in the treatment of cancer of reproductive tract origin" (*id.*).

16. Zhang states that "[s]ince 1960's, it has been reported both in China and the rest of the world that gossypol can be used as an antitumor drug" (Zhang 384).

17. Zhang discloses that gossypol "has the function of inhibiting DNA synthesis of the cells" (*id.*).

18. Zhang discloses that "(+) gossypol has no effect on the growth of HeLA [sic] cells at all; (±) and (–) gossypols can significantly inhibit the growth of HeLa cells; 5 μg/ml of (–)gossypol has the similar effect as 10 μg/ml of (±)gossypol, indicating that the functional part of the (±) gossypol is probably the (–) portion" (*id.* at 385).

19. Zhang discloses that "5 μg/ml or 10 μg/ml of (–) gossypol or 10 μg/ml of (±) gossypol . . . all can inhibit cell division, DNA synthesis and the function of re-proliferation of HeLa cells" (*id.* at 385-386).

20. Wu '86 discloses administration of (–)-gossypol to healthy men at a dose of 20 mg orally (Wu '86 614, left-hand col.).

21. Band '89 discloses a comparison of "the effects of racemic gossypol and the (–) and (+) isomers of gossypol on the proliferation of different human cell lines (both untransformed and cancer cell lines) of different tissue origins and mitogen-activated peripheral blood mononuclear cells" (Band '89 273, right-hand col.).

22. Band '89 reports that the "antiproliferative action of gossypol was not restricted to reproductive cancers, as non-reproductive cancer cell lines were also equally sensitive" (*id.*, abstract).

23. Band '89 states that "actively proliferating untransformed cells such as fibroblasts and PHA-activated lymphocytes were also sensitive" (*id.*).

24. Band '89 concludes that the "results demonstrate that gossypol *in vitro* acts as a general and nonselective antiproliferative agent and that the antiproliferative and other related activities of gossypol are primarily attributable to its content of (–) isomer" (*id.* at 276-277).

25. Band '89 states that, "[i]n view of a general antiproliferative activity of gossypol . . . , the lack of any reported *in vivo* side effects attributable to such an activity is surprising" (*id.* at 276, right-hand col.).

26. Dr. Reidenberg declares that "[s]uccessful anticancer drugs selectively kill tumor cells; if anticancer drugs killed cells indiscriminately, the cure would be worse than the disease" (Reidenberg declaration, ¶ 5).

27. Dr. Reidenberg declares that "[g]iven the general toxicity of gossypol to both normal and cancerous human cells *in vitro* as disclosed by Band ['89], one of ordinary skill in the art, upon reading that reference, would reasonably conclude that gossypol would be toxic to cancerous and noncancerous cells *in vivo*" (*id.* at ¶ 6).

28. Dr. Reidenberg declares that Rao[2] reported that "gossypol could be safely and effectively administered [to treat cancer in mice] within only a very narrow dosage range," because "although a dosage of 0.5 mg/mouse

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[2] Rao et al., 15 Cancer Chemother. Pharmacol. 20-25 (1985), of record.

was reportedly effective, . . . at 0.6 mg/mouse, nearly two-thirds of the mice died due to gossypol toxicity" (*id.* at ¶ 7).

29. Dr. Reidenberg declares that Tso[3] reported that "gossypol could be safely and effectively administered [to treat cancer in mice] within only a very narrow dosage range" because "[a]lthough a daily dosage of 25-100 μg of gossypol was found to be relatively safe and effective, . . . when the dosage was increased to 250 μg/day, all of the treated mice died due to gossypol toxicity" (*id.* at ¶ 8).

30. Dr. Holmlund declares that "[r]ecent findings support the expectation that (–)-gossypol is useful for the treatment of a wide diversity of cancers in humans" (Holmlund declaration, ¶ 3).

31. Dr. Holmlund declares that (–)-gossypol has been used in clinical trials to treat chronic lymphocytic leukemia, prostate cancer, and follicular lymphoma (*id.* at ¶¶ 5-7).

Principles of Law

Whether a claimed process would have been obvious under 35 U.S.C. § 103 depends on "whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art. Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure." *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988) (citations omitted).

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[3] Tso et al., 24 Cancer Letters 257-261 (1984), of record.

"Obviousness does not require absolute predictability of success. . . . For obviousness under § 103, all that is required is a reasonable expectation of success." *In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988).

"Indeed for many inventions that seems quite obvious, there is no absolute predictability of success until the invention is reduced to practice. There is always at least a possibility of unexpected results, that would then provide an objective basis for showing that the invention, although apparently obvious, was in law nonobvious." *Id.* at 903.

Expectation of success is assessed from the perspective of a person of ordinary skill in the art, at the time the invention was made. *See Life Techs. Inc. v. Clontech Labs. Inc.*, 224 F.3d 1320, 1326 (Fed. Cir. 2000).

Analysis

Claim 8 is directed to a method of treating cancer by administering (–)-gossypol. Wu '89 discloses that gossypol suppresses proliferation of human adrenocortical carcinoma cells in mice and that established tumors also responded to gossypol treatment. Band '86 discloses that cancer cell lines were significantly more sensitive to gossypol than normal cells, and that gossypol's (–) enantiomer had much more activity than its (+) enantiomer. Zhang discloses that (racemic) gossypol had been reported to be an antitumor drug, and that (–)-gossypol inhibits cell division, DNA synthesis and the proliferation of HeLa tumor cells. Wu '89 and Band '86 expressly suggest use of gossypol to treat cancer. We agree with the Examiner that the cited references would have suggested the method of claim 8 to those of ordinary skill in the art.

For a method to be obvious under § 103, however, the prior art must also provide a reasonable expectation of success. Appellants argue that this element of the prima facie case is lacking, because Band '89 discloses that gossypol has antiproliferative activity *in vitro* toward both cancer cells and noncancer cells. Appellants argue that this activity "teaches away from the treatment of cancer with (–)-gossypol as one of ordinary skill in the art would believe, based upon Band (1989), that (–)-gossypol would have significant side effects which would prevent the use of doses that are high enough [to] be useful for treatment of cancer" (Appeal Br. 6).

We do not agree with Appellants' interpretation of the evidence. Both Band '86 and Band '89 specifically state that administration of gossypol to humans (presumably as a contraceptive) did not result in side effects: Band '86 notes the "established absence of side effects in the administration of low doses of gossypol to humans" (Band '86 261), while Band '89 states that, "[i]n view of a general antiproliferative action of gossypol, . . . the lack of any reported *in vivo* side effects attributable to such an activity is surprising" (Band '89 276). Thus, the evidence does not support Appellants' position that those skilled in the art would have expected gossypol to cause significant side effects that would prevent its use to treat cancer.

In addition, Band '89 does not state that (–)-gossypol is toxic to all cells, only that it has a "general antiproliferative action." Band '89 therefore would have led those skilled in the art to expect that (–)-gossypol would kill normal proliferating cells (e.g., hair follicle cells and epithelial cells of the intestine), as well as proliferating cancer cells, but not that it would kill all types of cells indiscriminately. Appellants have not presented persuasive

evidence to support their position that (–)-gossypol's general antiproliferative activity – as opposed to indiscriminate toxicity – would have led those skilled in the art to expect that it would be ineffective in treating cancer. Rather, the evidence of record supports the Examiner's position that the prior art would have led those skilled in the art to reasonably expect (–)-gossypol to be an effective treatment for cancer.

Appellants also argue that the Reidenberg declaration shows that, because of gossypol's "narrow window of efficacy and safety" in mouse studies, those of skill in the art "would not have believed that it would have been possible to successfully determine a safe and effective dosage range in genetically heterogeneous humans" (Appeal Br. 6).

This argument is also unpersuasive. As discussed above, Band '86 and Band '89 disclose that use of gossypol in humans was known not to cause side effects, and Wu '89 and Band '86 expressly suggest use of gossypol to treat cancer in humans. These statements by persons of skill in the art contradict, and detract from the credibility of, Dr. Reidenberg's conclusion.

In addition, Appellants have presented no comparison of the results reportedly found by Rao and Tso with the results of studies using other drugs that either were developed as successful cancer treatments or were found to be too toxic to be used effectively to treat cancer in humans. The lack of context for the results described by Rao and Tso also casts doubt on whether Dr. Reidenberg's conclusion would be shared by a person of ordinary skill in the art.

Finally, even Dr. Reidenberg concedes that some of the dosages tested by Rao and Tso were safe and effective. Appellants have not adequately shown that, in view of the prior art as a whole, those of ordinary skill in the art would not have had a reasonable expectation of finding a dosage of (–)-gossypol that was effective in killing cancer cells in a human patient without also killing the patient.

Appellants also argue that the Holmlund declaration shows that "(–)-Gossypol has proven clinically effective in the treatment of several types of cancer in humans," and that its effectiveness is surprising "[i]n view of the experimental data reported in the prior art tending to show that (–)-gossypol would not be effective in the treatment of cancer in humans" (Appeal Br. 7).

This argument is not persuasive because, as discussed above, those of skill in the art would have reasonably expected (–)-gossypol to be an effective treatment of cancer. Appellants have not shown that its actual effectiveness is any greater than would have been expected based on the prior art.

In summary, the Examiner has shown that Wu '89, Band '86, and Zhang would have suggested the method of claim 8 and would have provided a reasonable expectation of success. Appellants have not shown any defect in the Examiner's prima facie case of obviousness, nor have they provided secondary evidence of nonobviousness to rebut it.

The Examiner also rejected claims 11-14 as obvious in view of Wu '89, Band '86, Zhang, and Wu '86 (Answer 6-7). The Examiner relies on Wu '89, Band '86, and Zhang for the disclosures discussed above, and finds that Wu '86 would have suggested, among other things, the oral dosage

recited in claim 13 (*id.* at 7). The Examiner concludes that the method of claim 13 would have been obvious in view of the combined teachings of the references (*id.*). We agree with the Examiner's reasoning and conclusion.

Appellants argue that:

> Wu (1986) . . . is of no consequence inasmuch as Wu (1986) does not satisfy the deficiencies of the other cited references as discussed above. In addition, . . . since the cited references do not disclose the additional features recited in claims 11-14, the present invention as defined by rejected claims 11-14 is even further removed from the prior art.

(Appeal Br. 8-9.)

These arguments are not persuasive. First, we do not agree with Appellants that the rejection based on Wu '89, Band '86, and Zhang has any deficiencies that must be remedied by Wu '86. Second, Appellants have not provided sufficient evidence or reasoning to support their position that the disclosure in Wu '86 of administration of (–)-gossypol as a single oral dose of 20 mg would not have suggested the limitation of claim 13 of oral administration of (–)-gossypol orally at a dose of 20-100 mg per day.

CONCLUSION OF LAW

The Examiner did not err in concluding that the prior art would have provided a reasonable expectation of success in administering (–)-gossypol to treat cancer in human patients.

SUMMARY

We affirm the rejection of claims 8-10, 16, and 38-43 under 35 U.S.C. § 103 based on Wu '89, Band '86, and Zhang; and the rejection of claims 11-14 under 35 U.S.C. § 103 based on Wu '89, Band '86, Zhang, and Wu '86.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

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